Mesenchymal stem cell-mediated ectopic hematopoiesis alleviates aging-related phenotype in immunocompromised mice.

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Public Summary:
Bone marrow mesenchymal stem cells (BMMSCs) are multipotent postnatal stem cells that are capable of differentiating into a variety of cell types, including osteoblasts, chondrocytes, adipocytes, and muscle cells. BMMSCs possess the capacity to form new bone and organize hematopoiesis when transplanted subcutaneously into immunocompromised mice using proper carriers. The recipientderived bone/marrow organ structures contain functional hematopoietic stem cells (HSCs), analogous to those from regular bones and are capable of rescuing lethally irradiated mice. Although it was postulated that multiple factors, including platelet-derived growth factor, basic fibroblast growth factor, and matrix metalloproteinase, may be involved in the BMMSC-mediated bone/marrow formation in vivo, the mechanism by which BMMSCs organize and support functional hematopoiesis is unidentified. In addition, the impact of ectopic bone marrow formation to whole body system is unknown. Clinically, BMMSCs have been used for the treatment of a variety of human diseases, including large segmental nonunion bone fractures, severe aplastic anemia, and acute graft-versushost disease, suggesting a feasibility of using BMMSC-organized hematopoietic progenitor source for stem cell–based clinical therapies. Subcutaneous transplantations of bone marrow mesenchymal stem cells(BMMSCs) are capable of generating ectopic bone and organizing functional hematopoietic marrow elements in animal models. Here we report that immunocompromised mice received subcutaneous BMMSC transplantations using hydroxyapatite tricalcium phosphate as a carrier suppressed age-related degeneration in multiple organs and benefited an increase in life span extension compared with control littermates. The newly organized ectopic bone/marrow system restores active hematopoiesis via the erythropoietin receptor/signal transducer and activator of transcription 5 (Stat5) pathway. Furthermore, the BMMSC recipient mice showed elevated level of Klotho and suppression of insulin-like growth factor I signaling, which may be the mechanism contributing to the alleviation of aginglike phenotypes and prolongation of life in the treated mice. This work reveals that erythropoietin receptor/Stat5 pathway contributes to BMMSC-organized ectopic hematopoiesis, which may offer a treatment paradigm of reversing age-related degeneration of multiple organs in adult immunocompromised mice.

Scientific Abstract:
Subcutaneous transplants of bone marrow mesenchymal stem cells (BMMSCs) are capable of generating ectopic bone and organizing functional hematopoietic marrow elements in animal models. Here we report that immunocompromised mice received subcutaneous BMMSC transplants using hydroxyapatite tricalcium phosphate as a carrier suppressed age-related degeneration in multiple organs and benefited an increase in life span extension compared with control littermates. The newly organized ectopic bone/marrow system restores active hematopoiesis via the erythropoietin receptor/signal transducer and activator of transcription 5 (Stat5) pathway. Furthermore, the BMMSC recipient mice showed elevated level of Klotho and suppression of insulin-like growth factor I signaling, which may be the mechanism contributing to the alleviation of aging-like phenotypes and prolongation of life in the treated mice. This work reveals that erythropoietin receptor/Stat5 pathway contributes to BMMSC-organized ectopic hematopoiesis, which may offer a treatment paradigm of reversing age-related degeneration of multiple organs in adult immunocompromised mice.